(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002537 A1

(51) International Patent Classification[7]: A61K 031/352, 031/36, A61P 033/10

(21) International Application Number: PCT/AU2003/000830

(22) International Filing Date: 26 June 2003 (26.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PS 3230 26 June 2002 (26.06.2002) AU

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/002537 A1

(54) Title: WORMING FORMULATION

(57) Abstract: A veterinary worming formulation comprising an effective amount of a macrocyclic lactone, together with an amount of piperonyl butoxide.

WORMING FORMULATION

The present invention relates to a veterinary formulation to effect broad spectrum worming in mammals and in particular to a synergistic combination of a macrocyclic lactone and piperonyl butoxide.

For many years it has been appreciated that macrocyclic lactones endectocides constitute reasonably effective antiparasitic formulations for a number of species including companion animals such as horses, cats and dogs and food animals such as sheep, cattle, pigs and goats. These compounds are also known to combat parasites in humans.

The dual activity of this class of compounds against endoparasites (anthelmintic) and ectoparasites (acaricide and insecticide) gave rise to the term endectocide. Macrocyclic lactones endectocides include two closely related groups of molecules: avermectins (e.g., ivermectin, abamectin, and eprinomectin) and milbemycins (e.g., milbemycin oxime and moxidectin). Such compounds are broad spectrum in the sense that they are active for example against large strongyles, small strongyles (cyathostomes), pinworms, roundworms (ascarids), hairworms, large mouth stomach worms, neck threadworms, heartworms, bots, lungworms and intestinal threadworms.

Relatively quickly over time however macrocyclic lactones in existing formulations reach peak concentration levels in the animal's blood and are then metabolised by the treated animals and cease to have activity against the target parasites. Relatively heavy dosage rates quickly

metabolise so that within one week of oral administration plasma sample analysis often reveals ineffective concentrations.

There is a need, therefore, for a macrocyclic lactone based worming formulation for mammals which facilitates elevated plasma concentrations of the macrocyclic lactone in the treated mammal.

Piperonyl butoxide, (The Merck Index, thirteenth Edition, Abstract 7557), is known to inhibit microsomal enzymes of insects and to extend, therefore, the activity of several insecticide preparations, especially the formulations which contain pyrethroids and rotenone.

The European patent EP 0 125 155 described the use of piperonyl butoxide as an insect metabolism inhibitor, in agricultural insecticidal, pesticidal and acaricidal combinations, together with certain naturally occuring avermectin product compounds or certain semi-synthetic derivatives thereof. The pesticidal formulations are used for controlling agricultural insect and mite pests of stored grain and agricultural plants in crops. The combination is useful in that the avermectin component has a long term efficacy at very low doses and the piperonyl butoxide has very rapid effects.

It has now surprisingly been found that a macrocyclic lactone compound exhibits an unexpected efficacy against helminthes parasites in mammals when administered simultaneously with or when formulated with piperonyl butoxide. We have found that this increased efficacy coincides with a more elevated plasma concentration of the macrocyclic lactone in

the treated animal when the macrocyclic lactone is administered together with piperonyl butoxide.

It is consequently an object of the present invention to provide a worming formulation which achieves longer lasting elevated plasma concentrations of macrocyclic lactones in mammals or at least provides the market with an alternative to existing formulations.

In one aspect, the invention provides a broad spectrum mammal worming formulation comprising an effective amount of a macrocyclic lactone, together with an amount of piperonyl butoxide as a synergist.

The term "worming formulation" as used herein means a formulation or a composition or a preparation for the prevention or the treatment of anthelmintic infestations in mammals.

In another aspect, the invention provides a method of prevention or treatment of anthelmintic infections in mammals consisting in administering substantially simultaneously to said mammals one macrocyclic lactone and piperonyl butoxide. The macrocyclic lactone and the piperonyl butoxide are administered either in the same composition or in two separate compositions which may be in different forms.

In still another aspect, the invention discloses the use of a formulation comprising a macrocyclic lactone, together with piperonyl butoxide in the manufacture of a medicament for the prevention or treatment of anthelmintic infections in mammals.

Macrocyclic lactone compounds include, for example, the avermectins and the milbemycins, or derivatives thereof, such as ivermectin, abamectin, eprinomectin, doramectin, milbemycin oxime, moxidectin. In a preferred embodiment, the macrocyclic lactone is abamectin. In another preferred embodiment, the macrocyclic lactone is ivermectin. In still another embodiment, the macrocyclic lactone is milbemycin oxime.

The present invention is suitable for treating the helminthes which occur in productive or breeding animals and pets. Illustrative but non-limiting examples of the animals are equines, bovines, felines, canines, swines, ovines. In a preferred embodiment, the worming preparation according to the present invention is administered to equidae and the invention provides a method of prevention or treatment of anthelmintic infections in equidae consisting in administering simultaneously to said mammals one macrocyclic lactone and piperonyl butoxide. In another preferred embodiment, the worming preparation is administered to dogs and the invention provides a method of prevention or treatment of anthelmintic infections in dogs consisting in administering simultaneously to said mammals one macrocyclic lactone and piperonyl butoxide. In still another preferred embodiment, the worming preparation is administered to sheep and the invention provides a method of prevention or treatment of anthelmintic infections in sheep consisting in administering simultaneously to said mammals one macrocyclic lactone and piperonyl butoxide.

Administration can be effected prophylactically as well as therapeutically.

In a preferred embodiment, the invention provides a method of prevention or treatment of anthelmintic infections in mammals consisting in administering simultaneously to said mammals abamectin and piperonyl butoxide. In another preferred embodiment, the invention provides a method of prevention or treatment of anthelmintic infections in mammals consisting in administering simultaneously to said mammals ivermectin and piperonyl butoxide. In still another embodiment, the invention provides a method of prevention or treatment of anthelmintic infections in mammals consisting in administering simultaneously to said mammals milbemycin oxime and piperonyl butoxide.

The active compounds are formulated and administered in the form of suitable preparations, enterally, parenterally, transdermally, nasally, or with the aid of articles such as, for example, strips, plates, bands, collars, ear marks, limb bands, marking devices including any controlled release devices.

The active compounds are administered enterally, for example orally, in the form of oral pastes, powders, tablets, capsules, drinks, granules, or solutions, suspensions and emulsions which can be administered orally, or as a bolus, medicated feed or drinking water. Oral pastes are particularly suitable forms for the administration of the formulations according to the invention to horses. Drenches are well suited for the administration of the formulations according to the invention to sheep.

Dermal administration is effected, for example, in the form of dipping, spraying or pouring-on and spotting-on. Parenteral administration is effected, for example, in the form of an injection (intramuscular, subcutaneous, intravenous, intraperitoneal) or by implants. Injectable compositions are suitable for the administration of the formulation according to the invention to dogs.

Suitable solvents, carriers, adjuvants and/or excipients depend of the chosen formulation and are well known by the skilled persons.

Optionally, the formulation may contain at least one other parasiticidal compound, including, but not limited to, anthelmintics, such as benzimidazoles, piperazine, levamisole, pyrantel, praziquantel and the like; endectocides such as avermectins, milbemycins and the like; ectoparasiticides such as arylpyrroles including chlorfenapyr, organophosphates, carbamates, gamabutyric acid inhibitors including fipronil, pyrethroids, spinosads, imidacloprid and the like; insect growth regulators such as pyriproxyfen, cyromazine and the like; and chitin synthase inhibitors such as benzoylureas including flufenoxuron, in order for example to further extend the spectrum of activity against other parasite species. In a preferred embodiment, the formulation according to the invention contains also an effective amount of praziquantel, a compound active against tapeworms.

The addition of other anthelmintic agents such as pyrantel, oxfendazole or the like would also provide a means of 'redundant' killing which is

known to limit the onset of resistance to a single action anthelmintic compound.

The preferred range of concentration for the macrocyclic lactone is such that the effective dose is from 0.02 to 2 mg per kg (mg/kg) of animal body weight. More preferably the dose is from 0.1 to 1.0 mg/kg of animal body weight.

The preferred dose range of piperonyl butoxide is from 0.2 – 20 mg/kg of animal body weight, preferably from 1 to 10 mg/kg of animal body weight and more preferably from 1 to 5 mg/kg of animal body weight.

The worming formulation of the present invention has been found to achieve elevated plasma concentrations of the macrocyclic lactone in the treated animal over time. The formulation according to the invention, has, therefore, the advantage of extending the activity of the macrocyclic lactone compound in the treated mammal. It prolongs the duration of the activity of the macrocyclic lactone and facilitates formulation of long acting veterinary compositions for the prevention or the treatment of anthelmintic infestations in mammals. It may also enable the use of reduced amounts of macrocyclic lactones, as active ingredients, while still providing effective anthelmintic prevention or control. The reduction in the amount of chemical agents introduced into the environment is an additional advantageous element of the subject invention.

Specific examples of formulations in accordance with the present invention will be described hereafter without limiting the generality of the invention as above described.

Example 1 :

Compound	Quantity g/L	Purpose
Macrocyclic Lactone*	6	Active Ingredient
Piperonyl Butoxide	30	Synergist
Praziquantel	45	Active Ingredient
Pyrantel Embonate	390	Active Ingredient
Excipient**	Qs to 1 litre	Vehicle

* The Macrocyclic Lactone can consist of abamectin, ivermectin, moxidectin, doramectin, eprinomectin or other members of the class of avermectin or milbemycin.

** The excipient base will consist of aqueous or organic solvent, preservative system, thickners, fillers, flavours colours or the like.

Example 2 :

Injectable formulations for cattle, sheep, cats or dogs.

Compound	Quantity g/L	Purpose
Macrocyclic Lactone*	6	Active Ingredient
Piperonyl Butoxide	25-175	Synergist
Thixcin R	1	Thickener
Sesame Oil	400	Vehicle/solvent
Myvacet 9-45 K	Qs to 1 litre	Vehicle/co-solvent

* The macrocylclic lactone can consist of abamectin, ivermectin, moxidectin, doramectin, eprinomectin or other members of the class of avermectin or milbemycin.

Example 3 :

Liquid oral formulation for sheep, goats, cattle, dogs and cats.

Compound	Quantity g/L	Purpose

Macrocyclic Lactone	0.5-5.0	Active Ingredient
Piperonyl Butoxide	2.5-25.0	Synergist
Other active ingredient	Optional	Active ingredient
Excipients	Qs to 1 litre	Vehicle/solvent/ stabilisers/thickner /etc.

Example 4 :

Tablet oral formulation for sheep, goats, dogs and cats.

Compound	Quantity g/L	Purpose
Macrocyclic Lactone	0.1-1.0	Active Ingredient
Piperonyl Butoxide	0.5-5.0	Synergist
Other active ingredient	Optional	Active ingredient
Excipients	Qs to 1 litre	Solvent/fillers/ stabilisers/etc..

Based upon the theory that the inclusion of piperonyl butoxide may increase the bioavailability of the macrocyclic lactone by inhibiting the hepatic metabolism of these compounds in the treated mammal, studies have been undertaken to evaluate the pharmacokinetic behaviour of a macrocyclic lactone based oral paste formulation in horses both with and without the addition of piperonyl butoxide.

The observed dual result is an elevation in the peak plasma concentration (Cmax) of the macrocyclic lactone and an increase in the area under the plasma curve (AUC) over time.

The increase in Cmax and AUC lead to a greater efficiency of the anthelmintic paste and allow lower doses to be administered and still be effective in removing parasites.

Trial 1 :

An existing oral paste formulation for control of worms in horses branded "Equimax" substantially comprising praziquantel and abamectin as actives was administered to six horses in the prescribed dosage. Six similar horses were dosed with the same Equimax formulation at the same dosage rate but in addition were treated with 10mg per kilogram of animal body weight of piperonyl butoxide.

The standard Equimax product was ascertained to contain the abamectin active at 3.7 g per litre (g/l) and praziquantel at 46.2 g/l and the dosage rate of the formulation was 1 ml per 20kg of animal body weight.

The piperonyl butoxide formulation contained piperonyl butoxide at a concentration of 500g/l and was administered at a rate of 2 ml per 100 kg of animal body weight.

The animals selected were horses being female thoroughbred or thoroughbred cross horses having a bodyweight between 320 and 465 kg and having no history of treatment with any macrocyclic lactone compounds within two months prior to the test. The horses were adults between the ages of 3 and 10 years.

All trial horses were grazed as a single group on a mix of native and improved pastures including rye grass, phalaris, fescue and white clover

in open grazing paddocks with constant access to water from dams and/or concrete troughs.

The trial horses were weighed on Day-5 and ranked in order of decreasing body weight and sequentially blocked into pairs. Horses were then randomly allocated from within each pair to the two treatment groups using numbered plastic tags randomly drawn from a plastic container. Allocation was such that each group had a similar group mean body weight and range of body weights within the group. The group mean body weight of the six horses treated with a formulation in accordance with the present invention was 376.5 kg whereas the group mean bodyweight of the group treated with standard Equimax product was 375.8 kg.

Duplicate 9 ml heparinized blood samples were taken from all horses prior to treatment and at 2, 4, 6, 8 and 12 hours post treatment and plasma harvested by high speed centrifugation and stored frozen on the day of administration.

The same sampling and harvesting method was repeated at 24 and 36 hours post treatment as well as at 48, 60, 72, 84, 96, 120, 144 and 168 hours post treatment.

The Group 1 horses comprising horses numbered 2, 3, 17, 78, 198 and 305 were administered with the Equimax and piperonyl butoxide formulations whereas the Group 2 horses were treated with standard Equimax. Group 2 comprised horses numbered 1, 4, 5, 109, 188 and 211.

The concentration of the active abamectin in the plasma samples at the abovementioned plasma sampling intervals is set out in tables 1 and 2 hereafter with table 1 being referable to Group 1 horses and table 2 referable to the Group 2 horses. Tables 1 and 2 show not only the concentration of abamectin in the plasma sample at the time of the particular sample but also the area under the curve generated by plotting the abamectin concentrations over the sampling times.

Plasma samples for all horses were analysed for their plasma abamectin levels by high performance liquid chromatography (HPLC) following extraction with ethyl acetate. The limit of detection with the analytical methodology used was 0.05 mg/mL and the limit of quantitation was 0.39 mg/mL.

Figure 1 appearing hereafter shows the group mean plasma concentrations in nanograms per millilitre of plasma for both Group 1 and Group 2 over the 168 hours of sampling.

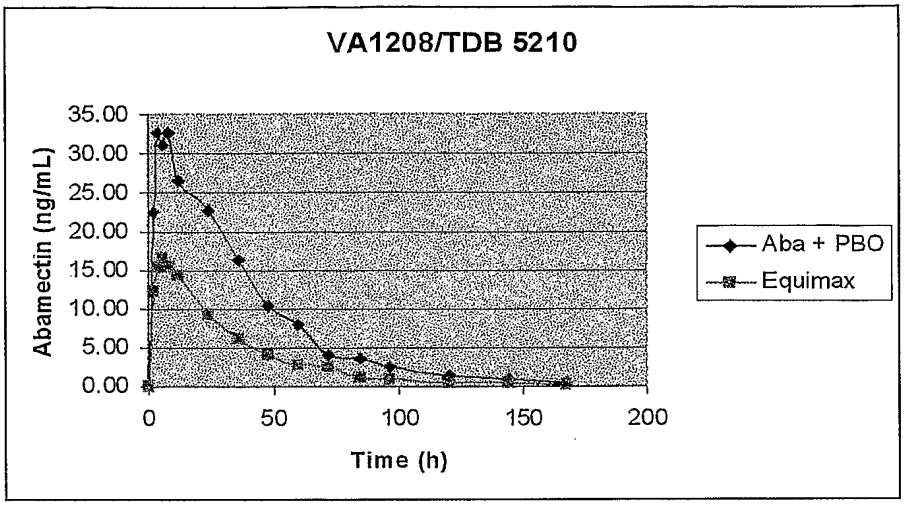

Figure 1: Abamectin Plasma-time response curves showing the AUC and Cmax for Equimax (Group 2) and Abamectin plus piperonyl butoxide (group 1)

Trial horses were observed for adverse reactions to either treatment for one hour post treatment and at each sampling point post treatment. No adverse reactions to treatment were noted.

From tables 1 and 2 appearing hereafter as well as figure 1 it will be observed that the Group 1 horses having been treated in accordance with the present invention exhibit plasma concentrations of the abamectin active significantly higher than those horses treated with Equimax alone and indeed the concentrations are approximately 100% higher at most sampling time intervals resulting in the area under the curves of Group mean plasma abamectin levels over time being of a similar superior order of magnitude as depicted in Figure 1.

Table 1: Concentration of abamectin from horses treated with abamectin plus piperonyl butoxide (PBO)

	Horse #		GROUP 1 Aba + PBO			
	2	3	17	78	198	305
Time (h)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)
0.0	0.00	0.00	0.00	0.00	0.00	0.00
2.0	0.56	19.03	44.69	33.63	10.82	26.67
4.0	2.06	33.04	55.28	29.85	23.29	53.06
6.0	2.63	24.95	45.17	19.11	34.59	60.20
8.0	1.62	29.13	49.96	23.12	33.58	59.55
12.0	4.32	18.54	36.69	11.91	31.47	57.00
24.0	32.86	9.06	21.13	5.95	22.74	42.97
36.0	26.66	3.24	15.73	3.77	14.01	34.00
48.0	15.15	1.21	11.29	2.11	8.67	23.93
60.0	10.33	0.56	8.80	1.48	8.44	17.22
72.0	1.15	0.28	6.74	0.99	3.26	12.37
84.0	3.64	0.16	5.34	0.62	2.09	9.29
96.0	2.16	0.14	4.49	0.51	1.36	6.67
120.0	0.82	0.00	2.66	0.32	0.98	3.34
144.0	0.32	0.00	1.88	0.23	0.42	2.36
168.0	0.18	0.00	1.37	0.19	0.17	1.26

Table 2: Concentration of abamectin in horses treated with Equimax.

	Horse #		GROUP 2 Equimax			
	1	4	5	109	188	211
Time (h)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)	Conc (ng/ml)
0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.0	3.49	12.14	23.28	24.81	8.47	1.28
4.0	9.84	16.44	20.29	20.58	21.16	4.60
6.0	14.88	14.33	13.82	14.71	27.16	17.84
8.0	14.89	15.87	17.59	17.50	29.26	7.10
12.0	14.98	21.01	9.78	11.66	23.42	23.46
24.0	12.66	10.54	6.18	8.65	13.63	12.15
36.0	7.93	5.86	4.23	7.19	8.10	8.21
48.0	4.67	3.22	3.08	5.74	5.50	5.21
60.0	2.33	2.32	2.34	4.43	3.75	3.10
72.0	6.12	1.20	1.76	3.45	1.99	1.89
84.0	0.55	0.85	1.28	2.53	1.25	1.06
96.0	0.36	0.52	1.06	2.20	0.72	0.78
120.0	0.00	0.25	0.74	1.40	0.37	0.30
144.0	0.00	0.13	0.58	0.94	0.13	0.14
168.0	0.00	0.00	0.40	0.80	0.07	0.07

Trial 2 :

In another study (VA073/TDB3360), groups of horses were treated with either Equimax as described earlier or with a liquid formulation containing abamectin and piperonyl butoxide as tabulated below.

Table 3: Groups and treatments in the study VA073/TDB3360

Group Number	Treatment	Abamectin dose µg/kg	Piperonyl butoxide mg/kg	Praziquantel mg/kg	Number of animals
1	Untreated	0	0	0	4
2	Equimax	200	0	2.5	4
3	Abamectin + pip but	200	10	0	4

Each selected horse was weighed and treated in accordance with a dosage rate tied to the individual animal's body weight. Treatments were administered orally. Throughout the study, animals were managed similarly to those described above.

Thirteen or fourteen days after treatment the animals were slaughtered for recovery of any parasitic worms in the gastrointestinal tract to evaluate the efficacy of the chosen formulation. Before slaughter, blood samples were taken for later evaluation of the plasma abamectin concentrations over time.

The results of the percentage efficiency are tabulated below.

Table 4: Percentage efficiency based on the estimated number of worms recovered from the lumen of the large intestine.

Group Number	Treatment	Number of small cyathostomes	Percentage efficiency
1	Untreated	51,500	
2	Equimax	4,000	92
3	Abamectin + pip but	0	100

Table 5: Percentage efficiency based on the estimated number of worms recovered from the wall of large intestine following pepsin digestion.

Group Number	Treatment	Number of small cyathostomes*	Percentage efficiency
1	Untreated	29.8	
2	Equimax	0.46	98
3	Abamectin + pip but	0.60	98

* Estimated by weighing total organ and subsampling a unit weight for digestion and counting.

Plasma samples were analysed for the concentration of abamectin similar to those described above. The results for AUC and Cmax are tabulated below.

Table 6: Area under the curve (AUC) and maximum concentration (Cmax)

Group Number	Treatment	Mean AUC ng/mL/hr	Cmax ng/mL
2	Equimax	346	14.2
3	Abamectin + pip but	953	40.2

The abamectin plasma-time response curves are illustrated below.

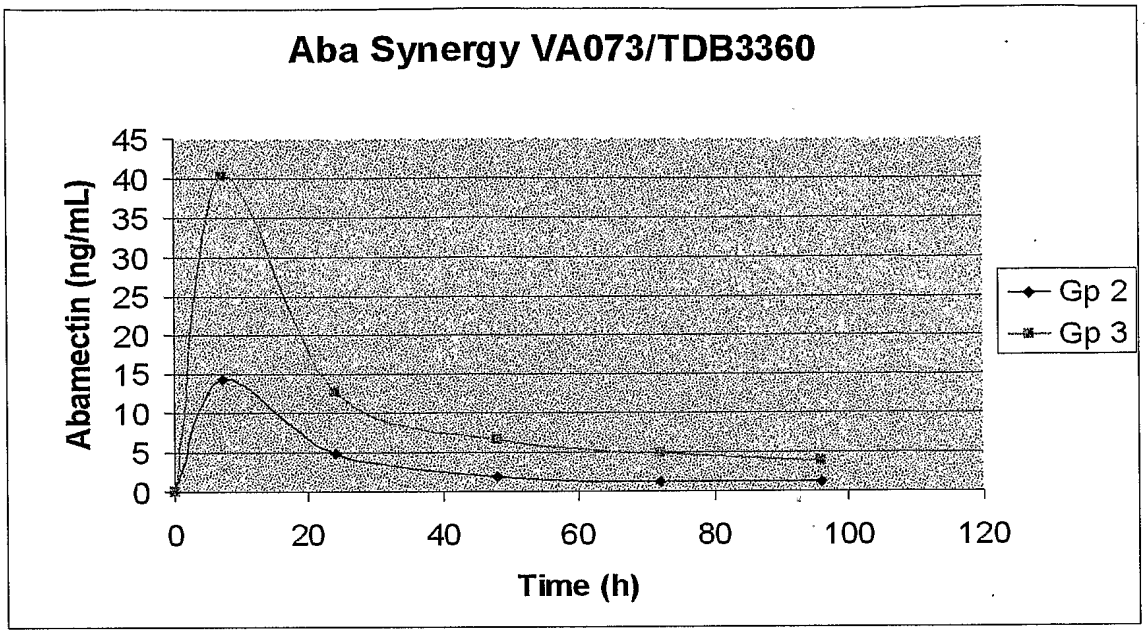

Figure 2: Abamectin Plasma-time response curves showing the AUC and Cmax for Equimax (Group 2) and Abamectin plus piperonyl butoxide (Group 3)

From Table 6 and figure 2, it will be observed that the mean of the Group treated with abamectin plus piperonyl butoxide had a higher mean AUC and Cmax than the group treated with Equimax alone.

Statistical analysis was performed on the data and it revealed a statistically significant difference between these two groups with respect to both AUC and Cmax.

Trial 3 :

This study aims to define the pharmacokinetic behaviour of the ivermectin component of an oral paste formulation containing different concentrations of piperonyl butoxide. This trials investigated oral paste formulations containing ivermectin, with varying quantities of piperonyl

butoxide in order to deliver to the animals respectively 0, 1 and 5 mg/kg of animal bodyweight.

This study comprises three groups of horses containing each six horses, which were treated with one of the three oral paste formulation. Allocation was such that each group had a similar group mean body weight and range of body weights within the group.

Each selected horse was weighed and treated in accordance with a dosage rate tied to the individual animal's body weight. Treatments were administered orally. Throughout the study, animals were managed similarly to those described in the trial 1. Moreover, We use the sampling and harvesting method described in the trial 1.

The group B horses were administered with the oral paste formulation delivering 0.2 mg/kg of ivermectin and 5 mg/kg of piperonyl butoxide.

The group C horses were administered with the oral paste formulation delivering 0.2 mg/kg of ivermectin and 1 mg/kg of piperonyl butoxide.

Finally, the group D horses were administered with the oral paste formulation delivering 0.2 mg/kg of ivermectin but no piperonyl butoxide.

The mean maximum concentration of the active ivermectin (Cmax) for each groups is set out in table 7. This table show not only the mean maximum concentration of ivermectin but also the mean area under the curve (AUC) generated by plotting the ivermectin concentrations over the sampling times.

Table 7 : Mean maximum concentration of the ivermectin and mean AUC for each group of horses.

Group of horses	Dose of PBO (mg/kg)	Peak	Time	AUC	n
B	5	54.46	6.33	3806	6
C	1	63.08	5.33	3898	6
D	0	49.11	8.33	3216	6

Notes : *Time* represents time to reach peak plasma concentration (hours)
Peak represents the peak plasma concentration in ng/mL
AUC represents area under the plot of concentration versus time using the linear trapezoidal approximation (ng/mL/h)

Trial horses were observed for adverse reactions to either treatment for one hour post treatment and at each sampling point post treatment. No adverse reactions to treatment were noted.

From table 7, it will be observed that the group B and C horses having been treated with a formulation in accordance with the present invention containing piperonyl butoxide exhibit mean AUC and mean Cmax higher than the group D horses treated with ivermectin alone.

The claims defining the invention are as follows:

1. A veterinary worming formulation comprising an effective amount of a macrocyclic lactone, together with an amount of piperonyl butoxide.
2. A veterinary worming formulation according to claim 1 wherein the macrocyclic lactone active is present at a concentration such that it may be administered to an animal at a dose of from 0.02 to 2 mg per kg of animal body weight.
3. A veterinary worming formulation according to claim 1 wherein the macrocyclic lactone active is present at a concentration such that it may be administered to an animal at a dose of from 0.1 to 1.0 mg per kg of animal body weight.
4. A veterinary worming formulation according to claim 1 wherein the macrocyclic lactone is ivermectin or abamectin or milbemycin oxime.
5. A veterinary worming formulation according to claim 1 wherein the piperonyl butoxide dosage is from 0.2 to 20 mg per kg of animal body weight.
6. A veterinary worming formulation according to claim 1 wherein the piperonyl butoxide dosage is from 1 to 10 mg per kg of animal body weight.
7. A veterinary worming formulation according to claim 1 wherein the piperonyl butoxide dosage is from 1 to 5 mg per kg of animal body weight.

8. A veterinary worming formulation according to claim 1 characterized in that said veterinary worming formulation is for oral use.
9. A method for preventing or treating anthelmintic infections in mammals, comprising administering substantially simultaneously to said mammals, a macrocyclic lactone and piperonyl butoxide.
10. A method according to claim 9 wherein the macrocyclic lactone and the piperonyl butoxide are in the same composition.
11. A method according to claim 9 wherein the macrocyclic lactone and the piperonyl butoxide are in separate compositions.
12. A method according to claim 9 wherein the macrocyclic lactone is administered at a dose of 0.02 to 2 mg per kg of animal body weight.
13. A method according to claim 9 wherein the macrocyclic lactone is administered at a dose of 0.1 to 1.0 mg per kg of animal body weight.
14. A method according to claim 9 wherein the macrocyclic lactone is selected from the avermectins and milbemycins or derivatives thereof.
15. A method according to claim 9 wherein the macrocyclic lactone is ivermectin or abamectin or milbemycin oxime.
16. A method according to claim 9 wherein the piperonyl butoxide is administered at a dose of 0.2 to 20 mg per kg of animal body weight.
17. A method according to claim 9 wherein the piperonyl butoxide is administered at a dose of 1 to 10 mg per kg of animal body weight.
18. A method according to claim 9 wherein the piperonyl butoxide is administered at a dose of 1 to 5 mg per kg of animal body weight.

19. A method according to claim 9 wherein the macrocyclic lactone and piperonyl butoxide are administered orally.

20. A method according to claim 9 wherein the macrocyclic lactone and piperonyl butoxide are administered in the form of an oral paste to equine animals.

21. A method according to claim 9 wherein the macrocyclic lactone and piperonyl butoxide are administered in the form of a drench to sheep.

22. A method according to claim 9 wherein the macrocyclic lactone and piperonyl butoxide are administered parenteraly.

23. A method according to claim 9, wherein the macrocyclic lactone and piperonyl butoxide are administered in the form of an injectable composition to dogs.

24. The use of a formulation according to claim 1, in the manufacture of a medicament for the prevention or treatment of anthelmintic infections in mammals.

25. The use of a formulation according to claim 24 in the manufacture of an oral paste for equine animals suitable to administered to said equine animal a dose of 0.1 to 10 mg per kg of animal body weight of the macrocyclic lactone and a dose of 1 to 5 mg per kg of animal body weight of piperonyl butoxide.

26. The use of a formulation according to claim 24 in the manufacture of an injectable composition for dogs suitable to administered to said dogs a dose of 0.1 to 10 mg per kg of animal body weight of the

macrocyclic lactone and a dose of 1 to 5 mg per kg of animal body weight of piperonyl butoxide.

27. The use of a formulation according to claim 24 in the manufacture of an oral drench for sheep suitable to administered to said sheep a dose of 0.1 to 10 mg per kg of animal body weight of the macrocyclic lactone and a dose of 1 to 5 mg per kg of animal body weight of piperonyl butoxide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/00830

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 031/352, A61K 031/36, A61P 033/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI and Chemical Abstracts keywords: macrocyclic()lactone, mectin, milbemycin?, avermectin, ivermectin, abamectin, eprinomectin, moxidectin, doramectin, milbemycin()oxime and piperonyl()butoxide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 125 155 A (MERCK&CO. INC.) 14 November 1984 See whole document	1-8, and 25-27
X	AU-A-11221/88 (GUERRINI, V. H.) 20 April 1989 See whole document	1-8, and 25-27
X	Derwent Abstract Accession No. 2003-523984, Class C02, CN 1401236 A (ZHAN/)ZHANG S 12 March 2003 See abstract	1-8 and 25-27

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2003	8 OCT 2003

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU03/00830

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
EP	0125155	JP	59219206	ZA	8402570
AU	11221/88		NONE		
CN	1401236		NONE		

END OF ANNEX